REMARKS

Upon entry of the amendment, claims 11-15, 18-20, 33-44, and 48-60 will be pending in the present application. Claims 11-15, 18-20, and 33-44 have been amended. Claims 48-60 have been added. The amendments and new claims do not add new matter within the meaning of 35 U.S.C. §132. Accordingly, entry of the amendments and new claims is respectfully requested.

Applicants take this opportunity to thank Examiner Sheikh for the Examiner Interview conducted on April 20, 2006.

The following Response is being filed to be fully responsive to the Official Action dated February 1, 2006.

1. Rejection of Claims 11-15, 18-20 and 33-43 under 35 USC §103(a)

The Official Action states that claims 11-15, 18-20 and 33-43 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Benton et al. (US Patent No. 4,876,094) in view of Wong et al. (U.S. Patent No. 6,120,803).

As the basis for this rejection, the Official Action states in relevant part:

> Benton *et al.* ('094) teach a dual coated liquid dosage formulation comprising dosage form cores such as matrix beads/microspheres (which can be time release or controlled release devises) containing a therapeutically active compound over which there are applied two unique coatings. These two coatings enable dispersion of the coated dosage form cores in a liquid carrier by imparting stability to the dosage form (see reference col. 1, line 55 - col. 2, line 20).
>
> Suitable controlled release type dosage form cores include controlled-release matrix beads/microspheres. The matrix beads/microspheres, typically are formed of a binder which is an insoluble material such as a soluble polymer or porous insoluble polymer or a wax which is intimately mixed with the therapeutically active compound (col. 3, lines 8-22).
>
> Ingestible materials useful as a binder include waxes such as paraffin, higher fatty acids, esters of fatty acids such as glyceryl tristearate, cetyl palmitate, diglycol stearate, glyceryl myristate, triethylene glycol monostearate, higher fatty alcohols such as cetyl alcohol and stearyl alcohol and higher molecular weight polyethylene glycols and mixtures thereof (col. 3, lines 23-36). The dosage form cores are microspheres or matrix beads coated with two materials. Most fats or glycerides include minor percentages of sterols, hydrocarbons, tocopherols and other non-glyceride constituents. The

fats or glycerides can include mono-, di-, or triglycerides (col. 3, line 67 - col. 4, line 14).

Alternative to a homogeneous mixture, a matrix bead/microsphere can be a core mixture of larger fragments of therapeutically active compound together with a binder. In another variation, the binder can envelop a fragment of therapeutically active substance forming a microsphere, which is essentially a microcapsule. Assorted and various matrix bead and microsphere configurations are suitable provided they do not substantially exceed 1400 micron diameter (col. 3, lines 47-59).

The dual coated microspheres/matrix beads are preferred dosage forms and have a size range of 15-300 μm (col. 5, lines 48-54). This range meets Applicant's claimed range of 50-500 μm. The controlled release microsphere/matrix beads can be prepared by microencapsulation processes including prilling, pan coating, granulation fluidization processes and other processes (col. 5, lines 60-66).

Therapeutically active ingredients are taught at col. 6, lines 41-50. Active ingredients taught include theophylline, antihistamines, cold formulations, analgesics, amino acid supplements, vitamins (*i.e.*, vitamin C), generic drugs, antidepressants and the like.

Benton *et al.* do not teach an active compound being an acid-labile proton pump inhibitor or a salt of an acid-labile proton pump inhibitor with a base or a hydrate of a salt of an acid-labile proton pump inhibitor with a base.

Wong *et al.* ('803) teach a prolonged release active agent dosage formulation adapted for gastric retention. The dosage formulation includes coated microspheres of an active agent or microspheres of an active agent and adjuvant, wherein especially suitable active agents are active agents for the localized treatment of gastric acidity and gastrointestinal disorders (i.e., duodenal/peptic ulcers; chronic gastritis) such as omeprazole and lansoprazole (see reference col. 18, line 1 - col. 20, line 12). Additional active agents include proteins, steroids, antidepressants, analgesics, antihistamines and the like.

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the proton pump inhibiting active compounds, such as omeprazole or lansoprazole taught by Wong *et al.* within the dosage formulation of Benton *et al.*, because Wong *et al.* teach that the active agents (*i.e.*, omeprazole, lansoprazole) are especially useful in their invention for the localized treatment of gastric acidity and gastrointestinal disorders, such as duodenal ulcers, peptic ulcers and chronic gastritis. The expected result would be an improved and effective proton pump inhibiting dosage formulation for the treatment of gastrointestinal disorders and conditions.

Applicants respectfully traverse this rejection. The references of record do not teach or suggest applicants' inventive subject matter as a whole as recited in the claims. The Examiner has failed to establish a *prima facie* case of obviousness against the presently rejected claim.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference. *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all

the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

Applicants respectfully submit that neither the Benton *et al.* reference nor the Wong *et al.* references cited in the rejection of claims 11-15, 18-20, and 33-43, taken alone or in combination, establish a *prima facie* case of obviousness against the presently pending claims. It would not have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the proton pump inhibiting active compounds taught by Wong *et al.* with the dosage formulations of Benton *et al* to arrive at the presently pending claims.

A. Present Claimed Subject Matter

The presently pending claims relate to an oral solid active compound unit comprising a microsphere, the microsphere comprising: a matrix comprising a mixture of at least one fatty alcohol and at least one solid paraffin; and an acid-labile active compound selected from the group consisting of an acid-labile proton pump inhibitor, a salt of an acid-labile proton pump inhibitor with a base, a hydrate of a salt of an acid-labile proton pump inhibitor with a base, wherein said acid-labile active compound is present in said matrix. Further, the presently pending claims relate to microspheres which comprise a matrix that contains at least one solid paraffin and at least one fatty alcohol as claimed in the present claims 11, 13-15, 33-41 and 44; or contain at least one

fatty acid ester or at least one triglyceride, and at least one solid paraffin as claimed in present claims 12, 42, and 43.

B. Disclosure of the Primary Reference

In contrast, Benton *et al.* is directed to an acidic liquid dosage formulation where the active compound is contained in the matrix of a dual-coated microsphere (col. 1, lines 13-15; col. 3, lines 1-5; col. 13, lines 45-51). Benton *et al.* requires the dual-coating in order to prevent release of the active compound into the acidic liquid carrier. See Benton *et al.* at col. 12, lines 60-68; and col. 16, lines 11-18. Benton *et al.* further requires that the acidic carrier comprise a sugar-based acidic liquid in order to achieve restricted release of the active compound. See Benton *et al.* at col. 13, lines 46-51, and claim 1.

C. Disclosure of the Secondary Reference

Wong *et al.* is directed to a dosage form that is retained in the stomach for prolonged periods of time to achieve prolonged delivery of an active agent in the stomach (col. 5, lines 29-33). Wong *et al.* achieves prolonged delivery in the stomach by providing a solid ingestible dosage form including an active agent and a polymer matrix formed of a mixture of a swellable, water soluble polymer that expands when in contact with fluids in the stomach and a water-insoluble hydroattractant (col. 5, lines 13-15). Wong *et al.* achieve prolonged retention time in the stomach by means of an

insoluble band which causes the polymer matrix to retain its integrity in an expanded state (col. 5, lines 30-34).

D. Differences between the References and the Presently Pending Claims

The presently pending claims require an oral solid formulation. In contrast, Benton *et al.* disclose a liquid dosage formulation which is entirely different both structurally and functionally than the presently claimed oral solids. Accordingly, Benton *et al.* do not teach the presently claimed oral solid formulations.

Wong *et al.* do not remedy this deficiency. In particular, the Wong *et al.* reference is directed to a completely non-analogous art area. Wong *et al.* is concerned with providing prolonged delivery of an active compound in the stomach by means of an insoluble band around a polymer matrix. In contrast, the presently claimed formulations deliver their active compounds in the intestines, because the claimed proton pump inhibitor actives decompose in an acidic environment (page 1, paragraph 3) such as is found in the stomach.

Therefore, it would not have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the proton pump inhibiting active compounds directed toward prolonged delivery in the stomach taught by Wong *et al.* with the liquid dosage formulations of Benton *et al.* to arrive at

applicants' oral solid formulation for delivery in the intestines.

Moreover, there is absolutely no suggestion that would motivate a person of ordinary skill in the art to combine the liquid dosage formulation of Benton *et al.* with the formulation described in Wong *et al.*, which is concerned with providing prolonged delivery of an active compound in the stomach, to arrive at the presently claimed solid dosage formulation which deliver their active compounds in the intestines.

Accordingly, reading Benton *et al.* in view of Wong *et al.* fails to show a suggestion or incentive that would motivate a person of ordinary skill in the art to combine as required by *In re Fine*.

Additionally, neither Benton *et al.* nor Wong *et al.*, taken alone or together, teach or suggest an active compound unit comprising a microsphere, where the microsphere matrix contains at least one solid paraffin and at least one fatty alcohol; or contains at least one fatty acid ester or at least one triglyceride, and at least one solid paraffin.

Accordingly, even combining the Benton *et al.* with the Wong *et al.* reference fails to teach or suggest all the limitations of the presently pending claims as required by *In re Wilson* and falls far short of beginning to establish a *prima facie* case of obviousness.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of pending claims 11-15, 18-

20, and 33-43 and allow these claims to proceed to grant.

2. Rejection of Claims 11-15, 18-20 and 33-44 under 35 USC §103(a)

The Official Action states that claims 11-15, 18-20 and 33-44 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Steber (US Patent No. 5,213,810) in view of Wong *et al.* (U.S. Patent No. 6,120,803).

As the basis for this rejection, the Official Action states in relevant part:

> Steber ('810) teaches stable microsphere compositions and methods of making microsphere compositions containing a fat, wax or mixture thereof; a biologically active protein, peptide or polypeptide; and an oil, semi-soft fat, fatty acid derivative or mixture thereof (see Abstract and Claims).
>
> A preferred embodiment involves the incorporation of the biologically active protein, peptide of polypeptide in fat or wax microspheres and oil or semi-soft fat which may optionally also contain some of all of the excipients described in column 4 (see col. 4, lines 43-57).
>
> The microspheres, preferably fat microspheres, may be up to 1,000 microns in diameter, with a weight average size range of 25 microns to 300 microns being preferred (col. 4, lines 43-57). This range meets Applicant's claimed range of 40-500 μm.
>
> The addition of a small amount of oil, semi-soft fat and/or fatty acid derivative to the mixture of fats and/or waxes and the biologically active protein, peptide or polypeptide before prilling allows for an increased stability microsphere composition (col. 2, lines 5-26).
>
> Waxes and fats suitable for the invention include hydrocarbons, esters of fatty acids and alcohols. Included are saturated or unsaturated long chain fatty acids, alcohols, esters, salts, ethers or mixtures

thereof (col. 2, lines 39-58).

Suitable waxes taught include fossil or earth waxes such as ozocerite and petroleum waxes such as paraffin, microcrystalline (col. 2, lines 60-68).

Fats include glyceryl esters of higher fatty acids such as stearic and palmitic. The fat is preferably composed of mono-, di-, or triglyceryl esters of long chain fatty acids. The mono-, di-, or triglycerides are composed predominantly of stearates, palmitates, laureates, linoleates, oleates and residues or mixtures thereof. Glyceryl tristearate is a most preferred fat (col. 3, lines 6-68).

The microspheres of the invention may be prepared by incorporating the active ingredient having the desired particle size, and other excipients with a molten fat, wax or mixture thereof, admixing the oil, semi-soft fat and/or fatty acid derivatives and then forming microspheres of the resulting mixture by a variety of techniques include atomizing prilling the mixture or by processing the mixture of ingredients of fat, wax or mixture thereof mechanically and cooling, for example utilizing a centrifugal disc. Alternatively, the mixture of active ingredients, excipients, fat, waxes and mixtures thereof and oil may be cooled to give a solid which may then be processed by procedures such as milling, grinding and the like (col. 5, lines 52-65).

According to Steber, mixtures of hard fats with liquid fats when melt blended and spray atomized to form prills or microspheres show accelerated transformation of alpha to beta crystal at room temperature and show markedly improved physical stability and exceptional attributes (col. 5, lines 3-15).

Active ingredients taught by Steber are biologically active protein, peptide or polypeptide.

Steber does not teach an active compound being an acid-labile proton pump inhibitor or a salt of an acid-labile proton pump inhibitor with a base of a hydrate of a salt of an acid-labile proton pump inhibitor with a base.

Wong *et al.* ('803) teach a prolonged release active agent dosage formulation adapted for gastric retention. The

> dosage formulation includes coated microspheres of an active agent or microspheres of an active agent and adjuvant, wherein especially suitable active agents are active agents for the localized treatment of gastric acidity and gastrointestinal disorders (*i.e.*, duodenal/peptic ulcers; chronic gastritis) such as omeprazole and lansoprazole (see reference col. 18, line 1 - col. 20, line 12). Additional active agents include proteins, steroids, antidepressants, analgesics, antihistamines and the like.
>
> It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the proton pump inhibiting active compounds, such as omeprazole or lansoprazole taught by Wong *et al.* within the dosage formulation of Steber. One of ordinary skill in the art would be motivated to do so because Wong *et al.* teach active agents that include omeprazole, lansoprazole and teach that these active agents (*i.e.*, omeprazole, lansoprazole) are especially useful in their invention for the localized treatment of gastric acidity and gastrointestinal disorders, such as duodenal ulcers, peptic ulcers and chronic gastritis. The expected result would be an improved and effective proton pump inhibiting dosage formulation for treating an array of gastrointestinal disorders.

Applicants respectfully traverse this rejection. As stated above, to establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, the prior art relied upon must contain a suggestion of incentive to combine a reference as required by *In re Fine*. Second, the proposed modification of the prior art must have a reasonable expectation of success as required by *Amgen Inc. v. Chugai Pharm. Co.* Lastly, the prior art references must teach or suggest all the limitations of the claims as required by *In re Wilson*.

Applicants respectfully submit that neither the Steber

reference nor the Wong *et al.* references cited in the rejection of claims 11-15, 18-20, and 33-44, taken alone or in combination, establish a *prima facie* case of obviousness against the presently pending claims. It would not have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the proton pump inhibiting active compounds taught by Wong *et al.* and noted above in Section C above, with the dosage formulations of Steber to arrive at the presently pending claims 11-15, 18-20, and 33-44.

A. Disclosure of the Primary Reference

Steber is directed to a liquid dosage formulation of controlled release microspheres for parenteral administration to an animal. See Abstract; col. 2, lines 30-31.

Further, Steber describes microspheres that comprise a fat or wax or mixtures thereof, and about 1% to 30% of an oil, semi-soft fat, fatty acid derivative or mixtures thereof. Specifically, in Examples 1-7, Steber describes microspheres that contain glyceryl tristearate which is the "fat or wax" component, and Miglycol (a neutral triglyceride oil), glyceryl distearate (a fatty acid ester), or triacetin (glycerol triacetate) which is the "oil, semi-soft fat, or fatty acid derivative" component. Examples 8 and 9 describe microspheres produced from glyceryl tristearate alone and stabilized microspheres produced from glyceryl tristearate and neutral triglyceride oil.

B. Differences between the References and the Presently Pending Claims

The presently pending claims, as noted above in Section A, the arguments of which are hereby incorporated by reference in their entirety, require an oral solid formulation. In contrast, Steber is directed to a formulation for parenteral administration to an animal, which is entirely different both structurally and functionally than the presently claimed oral solids. Accordingly, Steber does not teach the presently claimed oral solid formulations.

Wong *et al.* do not remedy this deficiency. In particular, the Wong *et al.* reference is directed to a completely non-analogous art area. Wong *et al.* is concerned with providing prolonged delivery of an active compound in the stomach by means of an insoluble band around a polymer matrix. In contrast, the presently claimed formulations deliver their active compounds in the intestines, because the claimed proton pump inhibitor actives decompose in an acidic environment (page 1, paragraph 3) such as is found in the stomach.

Therefore, it would not have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the proton pump inhibiting active compounds directed toward prolonged delivery in the stomach taught by Wong *et al.* with the parenteral administration of Steber to arrive at applicants' oral

solid formulation for delivery in the intestines.

Moreover, there is absolutely no suggestion that would motivate a person of ordinary skill in the art to combine the parenteral administration of Steber with the formulation described in Wong *et al.*, which is concerned with providing prolonged delivery of an active compound in the stomach, to arrive at the presently claimed solid dosage formulation which deliver their active compounds in the intestines.

Accordingly, reading Steber in view of Wong *et al.* fails to show a suggestion or incentive that would motivate a person of ordinary skill in the art to combine as required by *In re Fine*.

Additionally, neither Steber nor Wong *et al.*, taken alone or together, suggest an active compound unit comprising a microsphere, where the microsphere matrix contains a mixture of at least one solid paraffin and at least one fatty alcohol as claimed in present claims 11, 13-15, 33-41 and 44; or contains a mixture of a least one fatty acid ester or at least one triglyceride, and at least one solid paraffin, as claimed in the present claims 12, 42, and 43.

Further, none of the Examples of Steber illustrate a microsphere containing at least one solid paraffin as claimed in the present claims, let alone a microsphere containing at least one solid paraffin and at least one fatty alcohol as claimed in present claims 11, 13, 33-41, 44, 48, and 50-60. Specifically, the glyceryl tristearate exemplified in Steber is not a "solid

paraffin" and none of the triglyceride oil, glyceryl distearate, and glycerol triacetate, exemplified in Steber, are fatty alcohols.

Accordingly, even combining Steber with the Wong *et al.* reference fails to teach or suggest all the limitations of the presently pending claims as required by *In re Wilson* and falls far short of beginning to establish a *prima facie* case of obviousness.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of pending claims 11-15, 18-20, and 33-44 and allow these claims to proceed to grant.

CONCLUSION

Based upon the above amendments and remarks, the presently claimed subject matter is believed to be novel and patentably distinguishable over the prior art of record. The Examiner is therefore respectfully requested to reconsider and withdraw the rejections of pending claims 11-15, 18-20 and 33-44. Favorable action with an early allowance of the claims pending in this application is earnestly solicited.

The Examiner is welcomed to telephone the undersigned attorney if she has any questions or comments.

Respectfully submitted,

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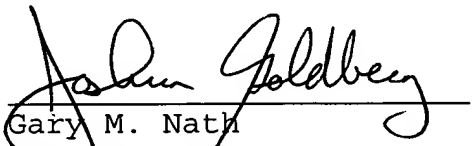

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